(13.85 mm^2) or ESP 24218 (11.7 mm^2) compared to mice receiving only saline injections (41.3 mm^2)($p<0.02$ for both comparisons). Atherosclerosis in mice expressing the control peptide (30.8 mm^2) was not significantly different than in mice receiving only the saline injection (p=ns). **Conclusion.** These results demonstrate an atheroprotective effect of ESP 24218, a 22 amino acid peptide designed to mimic the activity of ApoA-I, in mice.

1064-183 Endothelial Function and Carotid Intima-Media Thickness in Young Healthy Subjects Among Endothelial Nitric Oxide Synthase Polymorphisms

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Background: To assess the role of the endothelial nitric oxide synthase (eNOS) gene variants as risk factors for early atherosclerosis, we sought to investigate whether two polymorphisms located in the exon 7 ($Glu^{298}\rightarrow Asp$) and in the promoter region ($T^{-786}\rightarrow C$) of the eNOS gene were associated with functional changes in the endothelium, and carotid intima-media thickness (IMT).
Methods: Endothelium-dependent flow-mediated brachial artery dilation (FMD), endothelium-independent dilation response to glyceryl trinitrate (GTN), and carotid IMT were assessed by high resolution ultrasound in 98 healthy young non smoker subjects (29.8±0.5 years) genotyped for the eNOS $Glu^{298}\rightarrow Asp$ and $T^{-786}\rightarrow C$ polymorphisms.
Results: Carotid IMT was inversely related to FMD by univariate analysis (r=-0.29, p=0.003) and after adjustment for possible confounders in all the subjects (p=0.03). In comparison to Glu^{298} homozygotes, Asp/Asp carriers displayed a significantly lower FMD (Glu/Glu: 15.2%±1.2% vs Asp/Asp: 9.4%±1.7%, p=0.01), while FMD was unaffected by the $T^{-786}\rightarrow C$ variant (TT: 14.6%±1.1%, TC: 12.2%±0.8%, and CC: 12.0%±1.6%, p=0.18). Neither the $Glu^{298}\rightarrow Asp$ nor the $T^{-786}\rightarrow C$ polymorphisms influenced the GTN-mediated dilation.
Moreover, Asp/Asp genotype had a significantly greater carotid IMT than Glu allele carriers (Asp/Asp: 0.46±0.03 vs Glu/Glu: 0.38±0.02 and Glu/Asp: 0.36±0.01, p=0.001) and a strong inverse correlation between FMD and carotid IMT (Glu/Glu: r=-0.15, p=0.39; Glu/Asp: r=-0.18, p=0.23; Asp/Asp: r=-0.59, p=0.02). No difference in IMT was found across the eNOS $T^{-786}\rightarrow C$ genotypes (CC: 0.39±0.03, TC: 0.38±0.01, and TT: 0.38±0.02, p=0.98).
Conclusion: The eNOS $Glu^{298}\rightarrow Asp$ polymorphism may be related to early atherogenesis.

1064-184 Photodynamic Therapy Reduces Atherosclerotic Plaque Inflammation, Induces Plaque Stabilization and Promotes Plaque Reduction

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Background: Acute coronary syndromes are associated with other sites of vulnerable plaque located in areas of insignificant stenosis. Intravascular PhotoPoint™ photodynamic therapy (PDT) using light activation of the novel photosensitizer MV0633 is a potential treatment for these focal segments. Previous studies have shown cell depletion of plaque macrophages at 7 days post PDT. The aim of this study is to assess the potential of PDT to prevent re-infiltration of macrophages, stabilize plaques and promote vascular remodeling at 28 days.
Methods: New Zealand white rabbits (n=28) were fed a 1% cholesterol diet followed by bilateral iliac balloon endothelial denudation. At 5 weeks post-denudation, rabbits received photosensitizer MV0611 (3mg/kg I.V.) followed by light delivery using a Miravant catheter-based diode laser at 8 hours post-injection. Control animals received either drug or light alone. After PDT, rabbits received reduced cholesterol diet (0.05%) until sacrifice at 7 and 28 days. Arteries were sectioned every 0.5cm for a total of 16 sections/artery and morphometrically evaluated for vessel dimensions, cell poplulation and macrophage (Ram-11) and smooth muscle alpha actin content.
Results: At 7 days post PDT, plaque nuclei number decreased (PDT 766±231 versus control 3012±520mm^2, $P<0.001$) including significant loss of macrophages (PDT .37±0.13 v's 13.9±2.3% total plaque area, $P<0.001$). At 28 days, plaque macrophage area continued to be reduced with PDT treatment (PDT 0.5% v's control 8.7% total plaque area, $P<0.01$) and plaque area was significantly reduced by up to 44% (PDT 0.48± 0.05 v's control 0.86±0.16 mm^2) with no negative or positive arterial remodeling. At 28 days, plaque smooth muscle alpha actin content significantly increased (PDT 40.38±6.8 v's control 12.9±3.6% total plaque area) despite reduced plaque area.
Conclusions: Photopoint PDT promotes plaque reduction while simultaneously stabilizing plaques by changing plaque cellular composition from predominantly macrophages to smooth muscle cells.

1064-185 Systemic Infections Lead to Infiltration of Macrophages in Adventitia of Human Atherosclerotic Coronary Arteries: Clue to Triggering Effect of Acute Infections on Acute Coronary Syndromes

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Infections affect initiation and progression of atherosclerosis and trigger destabilization of vulnerable plaques. One third of acute myocardial infarctions follow an upper respiratory infection. The effect of systemic infections on human coronary artery atherosclerosis is largely unknown.
Methods: We studied the available pathology files of St. Luke's Episcopal Hospital between 1991 and 2002. After exclusion of patients with HIV infection, cancer, and those taking immunosuppressive drugs, 14 patients (11M, 3F, mean age: 67 yrs) with atherosclerosis and an acute infection prior to death (average 2 weeks) were selected. 13 pts (9M, 4F, mean age: 65 yrs) with atherosclerosis and without infection were selected as controls. Slides were stained with CD68 marker for macrophages (MQ). Plaque area was defined as the area inside the internal elastic lamina. Periadventitial fat was defined as up to 250 µm beyond the adventitia. MQ density was the number of MQ per square mm. Mann-Whitney U and Wilcoxon Signed Ranks tests were used.
Results: There was no significant difference in percent stenosis between cases and controls (67±14 vs. 55± 25, P=0.23). MQ density in plaques showed a non-significant trend toward higher levels in pts with systemic infection (582±774 vs. 281±321, P=0.41), however, there was a significantly higher number of MQ in adventitia of coronaries in pts with infection compared to controls (1,577±1,872 vs. 265±185, P=0.047). MQ density in periadventitial fat showed a non-significant trend toward higher levels in pts with systemic infection (776±821 vs. 212±219, P=0.085). Of interest, while MQ density in controls was not different between plaque and adventitia areas (281±321 vs. 265±185, P=0.85), MQ density in patients with systemic infection was significantly higher in adventitia than in plaque area (582±774 vs. 1,577±1,872, P= 0.028).
Conclusion: This report shows for the first time that systemic infections are associated with a significant increase in macrophage density in adventitia of human atherosclerotic coronary arteries. This suggests a mechanism for the triggering of AMI observed following acute infections, and offers a new therapeutic target for preventing heart attacks.

1064-186 Magnetic Resonance Imaging Detected Relationship Between Atherosclerotic Plaques and Shear Stress in Human Descending Thoracic Aorta In Vivo

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Background Atherosclerotic lesions preferentially develops at low shear stress (SS) locations. Although the descending aorta is known for its particular flow patterns, no previous studies have correlated wall thickness and shear stress in the descending thoracic aorta.Methods and results Cross sectional images of the thoracic descending aorta of 10 asymptomatic, hypercholesteremic, untreated patients were acquired utilizing a black blood sequence on a 1.5T clinical MRI system with a slice thickness of 5 mm and cross sectional resolution of 0.8 mm x0.8 mm. Atherosclerotic plaques were detected and the average wall thickness (WT) derived per quadrant. Quadrants were subdivided in four regions dependent on the distance (DA) from the aortic arch (region I: 1.0 cm <DA<=3 cm; Region II: 3 cm<DA<5 cm , Region III: 5 cm < DA< 7 cm , Region IV: 7 cm <DA < 9 cm). Average wall thickness was maximal at region I and statistical different from the most distal region (3.0±0.7 mm vs 2.5±0.3 mm; $P<0.05$). The atherosclerotic wall thickening showed a helicoidally pattern from the proximal to distal segments. Phase contrast MRI was performed in the thoracic aorta of 8 healthy volunteers, not aware of any atherosclerotic disease to derive a typical shear stress distribution. From the through plane velocity profiles the average shear stress was derived in the predefined quadrants as mean over the cardiac cycle. The atherosclerotic wall thickness showed to be inversely related to the shear stress : WT=-1.6*SS+3.3 [mm], r2=0.29, $p<0.05$). Normalization of the wall thickness (NWT) per region, emphasized that atherosclerotic plaque build up always starts and progresses at low shear stress regions (NWT = -0.019 * SS + 1.22 , r2=0.59, <0.05).Conclusion Our data showing a strong correlation between wall thickening and average low shear stress locations support the role of local hemodynamics in the development and progression of aortic atherosclerotic lesions.

1064-187 A Novel Metabolic Effect of Oxidized Low-Density Lipoprotein: Downregulation of Glyceraldehyde-3-Phosphate Dehydrogenase via a CD36 Scavenger Receptor-Mediated Redox Pathway Involving 5-Lipoxygenase

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Although oxidized LDL (OxLDL) exerts multiple proatherogenic effects, its effect on key metabolic pathways is unexplored. Glyceraldehyde-3-phosphate dehydrogenase (GAPDH) catalyzes the key glycolysis reaction and plays a major role in cell metabolism. To examine whether OxLDL regulates GAPDH in human aortic smooth muscle cells (HASMC), we exposed HASMC to 0-100 ug/ml $CuSO_4$-oxidized LDL or native LDL for 0-24 h. Western analysis and real-time PCR revealed dramatic OxLDL-specific time- and dose-dependent decreases in GAPDH mRNA and protein levels. GAPDH/actin protein ratios in response to 60 ug/ml of OxLDL were reduced by 65±18% (n=3) and 72±6% (n=6) at 6h and 15h, respectively. GAPDH protein expression at 24h was virtually not detectable and GAPDH mRNA level was reduced by 45±4% (n=3) at 15h with 60 ug/ml OxLDL. OxLDL reduced also GAPDH specific activity (52±6%, n=3) as assessed by measurement of NADH production. Blocking antibodies to CD36 scavenger receptor (20 ug/ml) reduced OxLDL-induced apoptosis (FACS analysis/annexin V staining) by 49% and significantly reduced OxLDL induction of peroxides and superoxides as assessed by CDC-H_2F diacetate and hydroethidine assays, respectively. Furthermore, anti-CD36 antibody completely inhibited OxLDL-induced reduction in GAPDH protein (n=6). The antioxidant Trolox (250 uM) completely inhibited OxLDL-specific peroxide, superoxide production (n=8) and decrease in GAPDH protein (n=3). Inhibition of cyclooxygenase-2 (NS-398, 10 uM) did not block OxLDL induction of superoxides nor reduction in GAPDH expression whereas 5 uM NDGA, a specific 5-lipoxygenase blocker, markedly inhibited OxLDL induction of superoxides (74±7%, n=8), peroxides (38±4%, n=8) and completely blocked OxLDL downregulation of GAPDH. In conclusion, OxLDL downregulates GAPDH mRNA, protein levels and enzyme activity in HASMC. This effect is mediated in large part via the CD36 scavenger receptor and a redox signaling pathway involving 5-lipoxygenase and contributes to the pro-apoptotic effect of OxLDL. These findings provide novel insights into metabolic effects of OxLDL on the vasculature and have major implications for understanding mechanisms of atherogenesis.